

## ABSTRACT

According to the present invention, eight human RING-CH-containing genes are human transmembrane ubiquitin ligase proteins, are homologues of the viral K3-family, and perform functions similar to their viral counterparts. One of these proteins, MARCH-IV, is able to downregulate MHC I and CD4 in a fashion similar to that afforded by the viral immune evasion proteins. This is the first cellular gene product identified that downregulates surface expression of MHC I. The MARCH-family of proteins regulates endocytosis of cell surface receptors (*e.g.*, transferrin receptor, histocompatibility antigens and Fas; type I as well as type II transmembrane domains) via ubiquitination. Particular embodiments provide drug targets for inhibiting the internalization and degradation of various cell surface receptors. Further embodiments provide methods for treating or preventing cancer and other disorders (*e.g.*, leukemia, mental retardation, and L-thalassemia), which methods comprise the administration of a MARCH antagonist or pharmaceutical composition thereof. Screening methods for identification of therapeutic compounds that are modifiers of MARCH activity, are also encompassed by the present invention.